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Thyroxine Values from Newborn Screening of 919 Infants Born before 29 Weeks' Gestation

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ABSTRACT

Objectives. Severe transient hypothyroxinemia in premature infants is associated with cerebral palsy and mental retardation; this study assessed its prevalence in very premature infants.

Methods. Congenital hypothyroidism screening programs in three states provided thyroxine values for 919 newborn infants younger than 29 weeks who were enrolled in a multicenter study.

Results. Thyroxine values were lower than 4.0 μg/dL in 21% of survivors and increased each week by 0.6 μg/dL (95% confidence interval [CI] = 0.4, 0.7). At tests done 1 to 2 days after birth, levels were 2.5 μg/dL higher (95% CI = 1.8, 3.3) than at tests done at 8 to 14 days. In New York, levels were 1.0 μg/dL higher (95% CI = 0.3, 1.6) than elsewhere. The levels of infants who died were 1.3 μg/dL lower (95% CI = 0.6, 2.0) than those of survivors.

Conclusions. Severe transient hypothyroxinemia is common in very premature infants and deserves further study. (*Am J Public Health.* 1997;87:1693–1697)

Introduction

Preterm infants often have low thyroxine levels postnatally, a condition referred to as transient hypothyroxinemia of prematurity.[1–13] Transient hypothyroxinemia of prematurity is a self-limited phenomenon thought to be caused by immaturity of the hypothalamic-pituitary-thyroid system and by changes in thyroid function that accompany severe illness, that is, nonthyroidal illness. Congenital hypothyroidism is not thought to explain why transient hypothyroxinemia is detected at newborn screening of premature infants because thyrotropin levels are normal. However, recent studies of preterm infants have linked very low thyroxine levels with abnormal cognitive and neurological development at ages 2 through 9 years.[14–18] It has been difficult to establish what represents a very low thyroxine level at any given gestational age because little is known about the gestational age–specific distribution of thyroxine values in very preterm infants. State screening programs tend to collect and report information classified by birthweight, not by gestational age,[12] and they rarely report quantitative results.

In this paper we describe thyroxine-screening findings in 919 preterm infants born before 29 weeks' gestation and enrolled in a multicenter study of cranial ultrasonographic abnormalities, the Developmental Epidemiology Network Study. These infants, whose gestational ages were established according to a study protocol, received intensive neonatal care in one of four nurseries in three states: Massachusetts, New Jersey, and New York. Quantitative thyroxine-screening results were obtained from state congenital hypothyroidism–screening programs and were assessed in relation to survival, postmenstrual and postnatal age at the time of screening, and site of care.

Methods

From January 1991 through December 1993, 1662 infants weighing 500 through 1500 g were systematically enrolled in a multicenter study of neonatal brain injury, the Developmental Epidemiology Network Study. Study infants were born in four hospitals in Massachusetts, New Jersey, and New York (two hospitals). Of the 919 born at less than 29 weeks' gestation, and therefore at high risk for severe transient hypothyroxinemia of prematurity, 746 survived to discharge from the intensive care nursery.

Gestational-age estimates were based on fetal ultrasound obtained before the 14th week of gestation (32%), dates in the prenatal record (62%), maternal postpartum interview (4%), and the admission logbook of the neonatal intensive care unit (2%).

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TABLE 1—Selected Characteristics of Newborn Thyroxine Screening in 917 Infants Born at 28 Weeks' Gestation or Less in Three Northeastern States

	Massachusetts	New Jersey	New York
Total no. enrolled	452	190	275
Died	86	40	47
Survived	366	150	228
Mean gestational age, wk (SD)			
Total	26.6 (1.6)	26.4 (1.8)	26.4 (1.6)
Died	25.4 (1.5)	24.8 (1.7)	25.3 (1.8)
Survived	26.8 (1.5)	26.8 (1.5)	26.6 (1.5)
Mean birthweight, g, (SD)			
Total	893.6 (217.2)	912.2 (243.6)	898.7 (227.7)
Died	746.6 (181.1)	707.3 (173.0)	740.0 (164.3)
Survived	927.9 (230.6)	966.8 (230.6)	931.5 (225.4)
Test results found, no. (% of total)			
Total	386 (85.4)	170 (89.5)	235 (85.5)
Died	36 (41.9)	23 (63.9)	21 (44.7)
Survived	350 (95.6)	147 (98.0)	214 (93.9)
Mean age at first test, d[a] (SD)			
Total	6.7 (9.8)	2.8 (4.3)	10.3 (11.0)**
Died	5.4 (5.6)	2.0 (0.4)	6.6 (6.6)**
Survived	6.8 (10.2)	2.9 (4.4)	10.6 (11.3)**
Mean thyroxine value,[a] μg/dL[b] (SD)			
Total	6.2 (2.8)	6.4 (3.1)	7.1 (3.7)*
Died	4.9 (2.6)	4.5 (3.4)	4.7 (2.9)
Survived	6.4 (2.7)	6.8 (2.9)	7.3 (3.7)*
Mean no. tests[a] (SD)			
Total	2.1 (1.1)	1.4 (0.8)	1.9 (0.9)**
Died	1.3 (0.7)	1.0 (0.0)	1.6 (0.9)*
Survived	2.2 (1.1)	1.4 (0.8)	1.9 (0.9)**
Thyrotropin tests done, no. (%)[a]			
Total	330 (85.5)	146 (85.9)	211 (89.8)
Died	35 (97.2)	21 (91.3)	19 (90.5)
Survived	295 (84.3)	125 (85.0)	192 (89.7)

[a]Among those infants for whom test results were found.
[b]To convert to nmol/L, multiply by 12.9.
*$P < .05$ and $> .001$; **$P < .001$.

Results for each study subject were obtained from the computerized thyroid-screening databases of each state and were linked to study subjects by matching on hospital, name, date of birth, and, where available in the state databases, birthweight. Postnatal age at testing was recorded.

Thyroxine and thyrotropin concentrations in dried blood spots collected on filter paper were measured by state laboratories. For Massachusetts, the laboratory was the Newborn Screening Laboratory; for New Jersey, the State of New Jersey Department of Health Inborn Errors of Metabolism Laboratory; and for New York, the Laboratory of Newborn Screening and Genetic Services, Wadsworth Center, New York State Department of Health. Thyrotropin assays were performed on the samples with thyroxine values in the lowest 10% of each run; in New Jersey, thyrotropin was also assayed when the thyroxine values were 1.3 standard deviations below the geometric mean or lower. Two cases of congenital hypothyroidism (both in Massachusetts) were identified among the study subjects, and these subjects were excluded. Study protocols were approved by the institutional review boards of involved institutions. SPSSPC+ (SPSS Inc, Chicago, Ill) was used to perform analysis of variance and chi-squared (two-tailed) tests of statistical significance of differences in continuous and categorical variables, respectively, and to estimate linear regression coefficients.

Results

Newborn thyroxine-screening values were located for 711 of 744 (96.6%) infants who survived to hospital discharge (Table I) and for 80 of 173 infants (46.2%) who died during the initial hospitalization. Of 711 survivors with test results, 287 (40%) had one test, 237 (33%) had two tests, 134 (19%) had three tests, 41 (6%) had four tests, 7 had five tests, and 5 had 6 tests.

For 12.5% of the subjects, the recorded sample date and the date of birth were the same. For 58.6% of the infants, the sample was obtained after the day of birth and within the first week; 16.5% were first tested in the second week of life, 6.6% in the third postnatal week, and 5.8% after the first 3 weeks.

Of the 700 infants who had thyrotropin values, 13 had values greater than 20 μIU/mL; all had repeat tests with thyrotropin values less than 20 μIU/mL.

Characteristics of Newborn Thyroxine Screening by State

Mortality rate, gestational age, birthweight, percentage of test results found, and percentage of tests subjected to thyrotropin determinations did not vary significantly by state. There were, however, significant differences by state in mean age at first test (Massachusetts, 6.7 ± 9.8 days; New Jersey, 2.8 ± 4.3 days; and New York, 10.3 ± 11.0 days; $P < .001$), mean thyroxine value (Massachusetts, 6.2 ± 2.8 μg/dL; New Jersey, 6.4 ± 3.1 μg/dL; and New York, 7.1 ± 3.7 μg/dL; $P < .05$), and mean number of tests per infant (Massachusetts, 2.1 ± 1.1 tests; New Jersey, 1.4 ± 0.8 tests; and New York, 1.9 ± 1.9 tests; $P < .001$).

Mean Thyroxine Values by Gestational Week among Survivors

For survivors, the mean thyroxine value increased from 5.1 ± 2.5 μg/dL among those born at 23 weeks' gestation to 7.8 ± 3.0 μg/dL in those born at 28 weeks' gestation (Table 2). At each gestational week, thyroxine values from infants in New York State tended to be higher than those for infants in Massachusetts and New Jersey. These findings were not altered by restricting the analysis to surviving infants screened in the first 2 weeks of life.

Percentage Distribution of Thyroxine Values by Week of Gestation among Survivors

The percentage of infants with screening thyroxine values of less than 4 μg/dL declined from 40.0% of those born at 23 weeks to 10.2% of those born at 28 weeks (Figure 1). The percentage of

TABLE 2—Mean Thyroxine Values (μg/dL),[a] by Week of Gestational Age, in 711 Survivors of Preterm Birth in Three Northeastern States

	Massachusetts		New Jersey		New York		Total Cohort	
Weeks' Gestation	No.	Thyroxine Level, μg/dL (SD)	No.	Thyroxine Level, μg/dL (SD)	No.	Thyroxine Level, μg/dL (SD)	No.	Thyroxine Level, μg/dL (SD)
23[b]	11	3.7 (2.5)	5	6.5 (0.7)	14	5.7 (2.5)	30	5.1 (2.5)
24	34	5.4 (2.5)	14	6.8 (2.5)	12	6.7 (3.6)	60	5.9 (2.8)
25	51	5.8 (2.6)	26	5.5 (3.5)	43	6.7 (3.9)	120	5.9 (3.3)
26	76	5.6 (2.6)	26	6.3 (3.4)	44	7.7 (3.0)	147	6.2 (2.9)
27	78	6.8 (2.7)	29	6.6 (2.3)	44	8.2 (3.6)	151	7.2 (3.0)
28	100	7.6 (2.4)	47	7.8 (2.8)	57	8.1 (4.1)	205	7.8 (3.0)
Total	350	6.4 (3.1)	147	6.8 (2.9)	214	7.3 (3.7)	711	6.7 (3.1)

[a]To convert to nmol/L, multiply by 12.9.
[b]The category 23 weeks includes 3 infants with gestational ages <23 weeks.

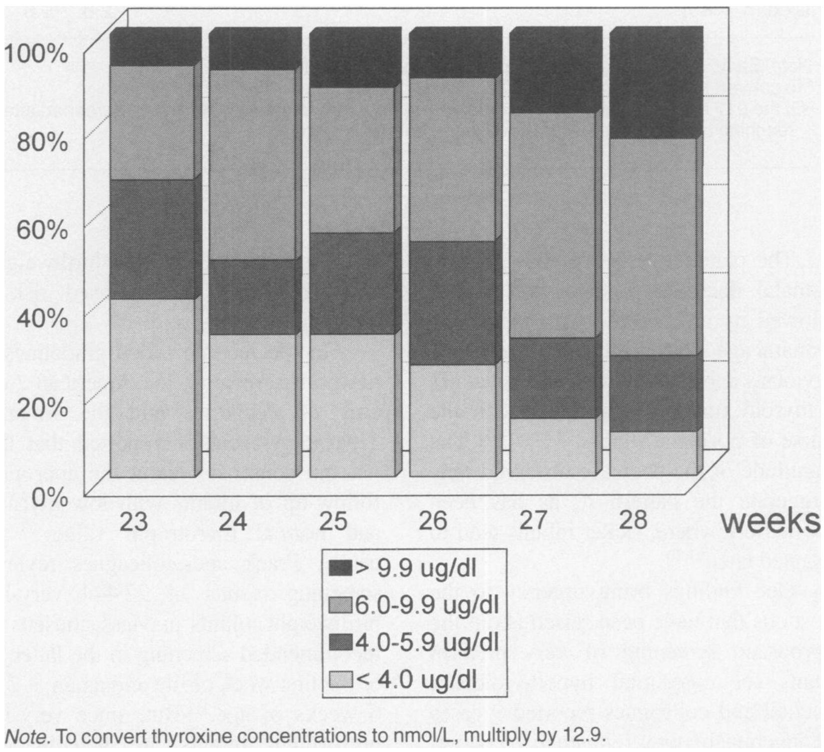
infants with screening thyroxine values greater than 10 μg/dL increased from 3% of those born at 23 weeks to 22% of those born at 28 weeks. Twenty-one percent of the survivors had initial thyroxine-screening values below 4 μg/dL.

Multivariate Model of Factors Associated with Screening Thyroxine Values

Thyroxine values increased 0.6 μg/dL per week (95% confidence interval [CI] = 0.4, 0.7) of postmenstrual age at screening (gestational age + postnatal age at screening) (Table 3). At a given postmenstrual age at screening, infants born within 2 days prior to the test had thyroxine values 2.5 μg/dL higher than those of infants who reached the same postmenstrual age at screening after 1 through 2 weeks ex utero (95% CI = 1.8, 3.3).

Even after adjustment for postmenstrual age and postnatal age at screening and mortality, infants at both New York hospitals had thyroxine values that were about 1.0 μg/dL higher than those of infants in Massachusetts and New Jersey (95% CI = 0.3, 1.6).

Infants who died (only 46.2% of whom were tested) had thyroxine values 1.3 μg/dL lower than those of infants who survived (95% CI = 0.6, 2.0).



Note. To convert thyroxine concentrations to nmol/L, multiply by 12.9.

FIGURE 1—Percentage distribution of newborn thyroxine-screening values in 711 survivors of preterm birth, by week of gestation.

Discussion

Older reports of newborn thyroxine-screening values did not include information about infants at less than 28 weeks' gestation,[1–4] and more recent studies have provided thyroxine values only on small numbers of very preterm infants.[13–17] In a previous study, which included 133 surviving infants born at 23 through 27 weeks and screened in New Jersey from 1984 through 1987, thyroxine values were similar to those reported here.[17]

The higher gestational age–specific thyroxine values in infants at the two New York hospitals may have been due to differences in the way the assay was performed. However, the differences occurred only in New York infants who survived; mean thyroxine values of infants who died did not differ by state. Thus, higher thyroxine values in New York may indicate lower morbidity for gestational age. Alternatively, New York infants may have had less exposure to iodine-containing antiseptics or may have experienced differences in feeding or respiratory-care practices. Differences between the Massachusetts site and one of the New York sites in care practices and rates of morbidity have been previously reported.[19]

TABLE 3—Associations of Postmenstrual Age and Postnatal Age at Screening, Site of Intensive Neonatal Care, and Mortality with Newborn-Screening Thyroxine Values (μg/dL)[a] Obtained in 781 Infants[b] Born at 28 Weeks' Gestation

	Linear Regression Coefficient	95% Confidence Interval
Postmenstrual age at screening (gestational age + postnatal age at screening; range, 23–32 wk)	0.6	0.4, 0.7
Postnatal age at screening, d		
0–2 (n = 312)	Referent	
3–7 (n = 250)	−1.4	−2.0, −0.9
8–14 (n = 131)	−2.5	−3.3, −1.8
>14 (n = 88)	−2.1	−3.0, −1.2
Hospital		
Massachusetts (n = 381)	Referent	
New York 1 (n = 136)	1.0	0.3, 1.6
New York 2 (n = 95)	1.1	0.4, 1.7
New Jersey (n = 169)	−0.4	−1.0, 0.2
Died (n = 80)	−1.3	−2.0, −0.6

Note. Each variable was adjusted for the others in the column.
[a]To convert to nmol/L, multiply by 12.9.
[b]Of the 917 research subjects, no screening values were found for 126, and 10 screened after reaching a postmenstrual age of 32 weeks were excluded.

The pattern we observed—an early postnatal decrease in thyroxine values, followed by an increase with increasing postnatal age—has been well documented previously and is thought to reflect changes in thyroid function associated with the course of postnatal illness.[1,3,5–7,9–11] The magnitude of the decrease observed may exaggerate the pattern if, as has been reported elsewhere, sicker infants tend to be tested later.[17,20]

Our findings bring urgency to the questions that have been raised about the appropriate screening of very preterm infants for congenital hypothyroidism. Mitchell and colleagues reported 9 cases of congenital hypothyroidism in very-low-birthweight infants (2 were in our sample) with very low thyroxine values but with thyrotropin values that did not become elevated until weeks to months after birth.[21] Apparently, immaturity and postnatal illness may temporarily depress the usual increase in thyrotropin concentrations that occurs with congenital hypothyroidism. These 9 cases in infants weighing less than 1300 g represented 13% of the 71 infants diagnosed with congenital hypothyroidism in New England from 1991 through 1993. Since infants weighing less than 1300 g are expected to compose less than 1% of neonatal survivors,[22] they are disproportionately represented among these cases, consistent with the possibility that very low birthweight is associated with an increased risk for congenital hypothyroidism.

In the recommended guidelines for newborn screening, the American Academy of Pediatrics and the American Thyroid Association reported that there was no consensus about the appropriate follow-up of infants with low thyroxine and normal thyrotropin values.[23] Recently, Frank and colleagues reviewed screening results of 22 444 very-low-birthweight infants in Massachusetts and recommended screening in the latter part of the first week of life and again at 2 and 6 weeks of age.[12] But, since very-low-birthweight infants are heterogeneous with respect to gestational age[24] and are therefore heterogenous in the degree of maturation of the hypothalamic-pituitary-thyroid system, screening protocols specific to different gestational ages may be required. To avoid missing cases of congenital hypothyroidism, and to establish the true prevalence of congenital hypothyroidism in very preterm infants, it would seem prudent to establish well-monitored protocols to repeat thyroxine and thyrotropin screening until thyroxine values reach normal levels.

Until recently, severe transient hypothyroxinemia in preterm infants has been viewed mainly as a source of false-positive tests in state congenital hypothyroidism thyroxine-screening programs. However, transient hypothyroxinemia in premature infants may be a significant public health problem in its own right, distinct from congenital hypothyroidism. Among children born preterm, severe transient hypothyroxinemia of prematurity has been associated with adverse motor and cognitive outcomes in the absence of congenital hypothyroidism in several studies.[14–18] The question of whether thyroxine administered to severely hypothyroxinemic preterm infants could prevent or modify neurodevelopmental problems is as yet unanswered. In a recently reported clinical trial, the neurologic development at age 2 did not differ between those who as infants of less than 30 weeks received thyroxine supplementation (infants were supplemented without regard to baseline thyroxine levels) and those who as infants received placebo.[25] However, the study lacked statistical power to detect a beneficial effect among severely hypothyroxinemic infants.

In summary, severe transient hypothyroxinemia, a condition that has been associated with increased risk for cerebral palsy and mental retardation in preterm infants, is common shortly after premature birth, and its consequences deserve further study. Congenital hypothyroidism screening programs will continue to be an important source of data about this condition. Future observational research would be facilitated if screening programs recorded gestational-age information on all screened infants, reported thyroxine values quantitatively, and required repeat testing until thyroxine values reached the normal range. □

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